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# Imaging of prehospital stroke therapeutics

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## Abstract

Despite significant quality improvement efforts to streamline in-hospital acute stroke care in the conventional model, there remain inherent layers of treatment delays, which could be eliminated with prehospital diagnostics and therapeutics administered in a mobile stroke unit. Early diagnosis using Telestroke and neuroimaging while in the ambulance may enable targeted routing to hospitals with specialized care, which will likely improve patient outcomes. Key clinical trials in Telestroke, mobile stroke units with prehospital neuroimaging capability, prehospital ultrasound and co-administration of various classes of neuroprotectives, antiplatelets and antithrombin agents with intravenous thrombolysis are discussed in this article.

### Keywords

stroke; prehospital therapeutics; mobile stroke unit; telemedicine; thrombolysis

## INTRODUCTION

Thrombolysis with intravenous tissue plasminogen activator (IV-tPA) within a 3 to 4.5-hours window following onset of symptoms for acute ischemic stroke reduces long-term disability [1–4], however, the benefits are time dependent with the chances of a favorable outcome falling twofold for every 90-minute delay in treatment [5–7]. Despite two decades of multi-pronged approach to improve tPA administration including the Joint Commission on Accreditation of Healthcare Organizations (JCACHO) accrediting “Primary Stroke Centers” [8], nationwide quality improvement measures such as the Get With the Guideline-Stroke (GWTG) registry [9] reveal that only about 5% of stroke patients received tPA, and most are treated beyond 2 hours from symptom onset when tPA is less effective [9–11]. With recent overwhelming evidence supporting the use of intra-arterial (IA) thrombectomy in addition to IV thrombolysis for large-vessel occlusive stroke [15–19], leaders in acute stroke care are revamping efforts to minimize time to treatment including prehospital therapeutics, patient

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selection for late reperfusion therapy using efficient neuroimaging, with prehospital neuroprotection, collateral and thrombolysis enhancement to support threatened tissue until reperfusion takes place.

A main reason for treatment delay may be lack of public recognition of stroke symptoms to seek care [20, 21], yet we consider other potential factors in this article. Other important factors within the control of physicians and other health care personnel include in-hospital delays (time to imaging, obtaining consent, time to laboratory studies), and improved access to stroke expertise at smaller community hospitals. The focus of this review is prehospital acute stroke therapeutics to shorten the time to treatment and preserve penumbra or tissue at risk. Key clinical trials in telestroke with transmission of neuroimaging, mobile stroke units with prehospital neuroimaging capability, and prehospital ultrasound and co-administration of various classes of neuroprotectives as well as antiplatelets and antithrombin agents with tPA thrombolysis are discussed below.

## CONVENTIONAL IN-HOSPITAL VERSUS PREHOSPITAL MODELS

Only 15–60% of patients with stroke arrive at the hospital within 3-hours after the onset of symptoms and even less within 2-hours when IV thrombolysis is most effective [22, 23]. Despite significant quality improvement efforts to streamline in-hospital acute stroke care in the conventional model, there remain inherent layers of treatment delays (door-to-needle time, DTN) such as time to assessment, time to neuroimaging and laboratory studies, and time for consent, which could all be eliminated with prehospital diagnostics and therapeutics administered in a mobile stroke unit. Such a prehospital strategy was first proposed in 2003 [24] and gradually developed along with advancements in reliable wireless telecommunication in 2010 [25], and finally led to publication of the landmark trial done in Germany: Prehospital Acute Neurological Treatment and Optimization of Medical care in Stroke Study (PHANTOM-S) [26] in 2014. There are at least three mobile stroke units in the United States (Houston, Cleveland, Denver) with centers around the globe now reorganizing treatment algorithms to incorporate prehospital stroke care customized to their community.

Figure 1 shows different approaches of conventional in-hospital (standard/current practice) and pre-hospital acute stroke management. With a CT scanner in the ambulance, non-contrast head CT, CT angiography and CT perfusion (in the future MRI) allow early diagnosis of ischemic vs hemorrhagic stroke vs stroke mimics of which the treatment pathways are completely different. A point-of-care laboratory system in the ambulance for glucose, coagulation panel (biomarkers to differentiate ischemic from hemorrhagic strokes in the future) will allow prehospital tPA (Figure 1, “ambulysis concept) and, in foreseeable future, prehospital neuroprotective agent administration (Figure 1, “freezing concept”).

Apart from administering prehospital thrombolysis and neuroprotectives, early diagnosis also enables disease-specific management in the field, and early triage with targeted ambulance routing to hospitals with specialized care such as routing patients with large-occlusive strokes to comprehensive stroke centers with endovascular intervention capability, or patients with intracranial hemorrhage to hospitals with neurosurgery capability, which may in turn save valuable time for additional hospital transfers [27]. For instance, in cases of

intracerebral hemorrhage from oral anticoagulants, rapid reversal of anticoagulation (international normalized ratio [INR] < 1.4) and blood pressure lowering (systolic blood pressure [SBP] < 160 mmHg within 4 hours of symptom onset have been shown to attenuate hematoma expansion (hematoma expansion in the intervention vs control groups 18.1% vs 44.1%, odds ratio [OR] 0.25, 95% confidence interval [CI] 0.19–0.42 and lower in-hospital mortality (13.5% vs 20.7%, OR 0.60, 95%CI 0.37–0.95) [28]. Given the limited therapeutic window for effective interventions, rapid transfusion of blood products or rapid administration of nicardipine drip could theoretically be all started in the ambulance.

Emergency Medical Service (EMS) personnel training in stroke triage is imperative in both conventional and prehospital models. Several prehospital stroke scales exist, each with unique qualities, sensitivity and specificities. In the USA, the Los Angeles prehospital stroke scale (LAPSS) and the Cincinnati prehospital stroke scale are most commonly used. In Europe the Face Arm Speech Time (F.A.S.T.) scale is most widely used. LAPSS contains four history items and a blood glucose measurement with the sensitivity of 91% and specificity of 97% [29] but it is time-consuming. Subsequently, Los Angeles Motor Scale (LAMS) [30] is adopted from the original LAPPS score (range from 0 to 10, higher scores indicating more severe motor weakness) is simple and fast to administer. The Cincinnati prehospital stroke scale evaluates the presence or absence of facial palsy, asymmetric arm weakness, and speech disturbance (by having the patient repeat a sentence) with sensitivity of 90% and specificity of 66% in diagnosis of stroke [31]. F.A.S.T. scale includes three key elements from the Cincinnati scale (facial weakness, arm weakness, and speech disturbance) has a sensitivity of 79% and a positive predictive value of 78% [32]. Regardless of the scale, the instrument needs to be easy to use by the EMS personnel to enable rapid and accurate stroke triage.

## TELESTROKE

There is significant geographic disparity in tPA administration in part due to shortage in physicians specializing in acute stroke management, particularly in smaller, rural underserved community hospitals [10, 33]. The shortage will likely get worse with the growing burden of stroke in an aging population [34]. In the United States, for instance, only 55% of Americans have access to primary stroke centers within 60-minute drive time, and nearly half of all hospitals have fewer than 100 beds most with no staff neurologists [35]. Accordingly, patients with acute ischemic stroke presenting to rural emergency departments are about 10 times less likely to receive tPA than those presenting to urban primary stroke centers [35]. Telestroke may offer a solution to limited access of stroke expertise that enables remote clinical evaluation, thereby allowing optimal treatment and management even in clinically underserved areas and removing geographical disparities in access to expert care [36]. In addition to assistance in decision for thrombolysis in resource limited regions, telestroke may also facilitate appropriate transfer of patients with complex conditions (who require neurocritical care services and neurosurgical or intra-arterial interventions) to a comprehensive stroke center.

## Telestroke structure and trends

The term “telestroke” was coined in 1999 soon after the dawn of the thrombolysis era in stroke medicine [37]. It is an application of video telecommunications to facilitate consultations by stroke specialists remote from stroke patients [38–42]. Key components of telestroke are high-quality video teleconferencing, transmission of digital imaging and communication of medical imaging data (primarily from CT and MRI). Telestroke can also incorporate the capacity for decision-support software, training of medical personnel, data storage and retrieval, creation of documentation for billing purposes, and integration with hospital emergency services. Initially, TeleStroke networks developed slowly, mainly in the United States, Germany and France [43–46]. These networks showed that telemedicine can increase the frequency of tPA administrations and also showed its safety [38, 46, 47]. In 2006, improved outcome was found in a controlled study comparing hospitals with and without TeleStroke Units [38, 48]. Since then telestroke became an increasing means throughout the world to bring stroke expertise to resource limited regions [49]. Different network structures were developed, taking into account particular characteristics of local health-care systems, geography and population [50]. The hub and spoke model, for instance, is centered on the large tertiary medical centers, known as hub hospitals, have access to resources not available to smaller spoke hospitals, making telestroke consultation mutually financially beneficial [51, 52]. In this model, the tertiary medical center has a rotating call schedule with a large group of trained vascular neurologists to respond to the telestroke consultations [51, 52]. This provides spoke hospitals continuous access to specialty evaluation for acute stroke patients. Today, TeleStroke is a rapidly growing field with more than 40 networks described in the literature [50]. The most frequent utilization of telemedicine in stroke care is remote consultation regarding thrombolytic treatment and/or patient transfer to a tertiary stroke center [2, 49, 53].

## Impact of telestroke on stroke system-of-care and clinical outcomes

Studies have shown increased tPA administration in smaller community with reduced time to treatment, improved stroke dependency and safety with the use of telestroke [38, 46–48]. Hospitals using stroke telemedicine typically report tPA rates of ≈15% (compared to ~5% without telestroke) with rates ≥50% in eligible patients with acute ischemic stroke [54–56].

Telemedical Project for Integrative Stroke Care (TEMPiS) is a nonblinded, nonrandomized intervention study in Bavaria aimed to assess the effects of a stroke network with telestroke on quality of care, according to acute processes and long-term outcome [48]. Five community hospitals with telestroke (supported by two academic hospitals) were matched with five community hospitals without telestroke support. All patients with stroke admitted within a 2-year period were eligible for inclusion in the study, of whom 3,122 were included in the final analysis. Poor outcome was defined by death, institutional care, or disability (Barthel index <60 or modified Rankin scale >3). After 3 months, significantly fewer patients treated in telestroke network hospitals than in the control hospitals had a poor outcome (44% versus 54%, P<0.0001). In a multivariate regression analysis, treatment in telestroke network hospitals was an independent predictor of reduced probability of a poor outcome (OR 0.62, 95% CI 0.52–0.74; $P$ <0.0001). The benefit for telestroke sustained

throughout 30 months of follow-up, and was associated with a significant reduction in death and dependency [48].

However, it is not uncommon that a telephone consultation (instead of televideo-stroke consultation) with an emergency department physician is used to make the decision of whether or not to administer tPA to patients. Meyer et al. [58] prospectively assessed whether telemedicine or telephone was superior for decision making in acute telemedicine consultations in a randomized trial conducted in California (Stroke Team Remote Evaluation using a Digital Observation Camera [STRoKE DOC]). They found that correct treatment decisions were made significantly more often in the telestroke group than in the telephone consultation group (98% versus 82%, OR 10.9, 95% CI 2.7–44.6) [59]. There was no difference between the groups in 90-day clinical outcomes, although this study was underpowered to detect differences in functional outcomes. A pooled analysis of data from a multistate telestroke network in California and Arizona, which included 54 patients from Arizona randomly assigned to each treatment group, reinforced the finding of superiority of telestroke over telephone consultation in clinical decision-making [54]. Subsequently, the American Stroke Association recommends that a stroke specialist, using high-quality video teleconferencing, should provide a medical opinion in favor of or against the use of intravenous tPA in patients with suspected acute ischemic stroke when onsite stroke expertise is not immediately available (class I recommendation, level of evidence B) [49].

## Telestroke feasibility and reliability

Reliability of the NIHSS-telestroke in controlled environments such as the outpatient or non-acute setting does not necessarily imply reliability in the more chaotic environment in which acute stroke interventions such as thrombolytic therapy are provided. Multiple studies have shown good reliability between in-person vs telestroke evaluation of acute stroke in both simulated scenarios in the ambulance [60] and real-time cases [41, 43–45, 58]. In a pilot prehospital telestroke simulation study, Prehospital Utility of Rapid Stroke Evaluation Using In-Ambulance Telemedicine (PURSUIT), Wu et al. [60] in Houston tested 10 scripted stroke simulation scenarios, each conducted 4 times by trained actors retrieved and transported by Houston Fire Department emergency medical technicians to a designated medical center. In 34 of 40 (85%) scenarios, the teleconsultation was conducted without major technical complication. The absolute agreement for intraclass correlation was 0.997 (95% CI, 0.992–0.999) for the NIH Stroke Scale obtained during the real-time sessions and 0.993 (95%CI, 0.975–0.999) for the recorded sessions. Interrater agreement using κ-statistics showed that for live-raters, 10 of 15 items on the NIH Stroke Scale showed excellent agreement and 5 of 15 showed moderate agreements. Matching of real-time assessments occurred for 88% (30/34) of NIH Stroke Scale scores by ±2 points and 96% of the clinical information [60].

Similarly in real-time telestroke cases, Bergrath et al [61] in Germany reported that teleconsultation on patients with suspected stroke was feasible but that there were no differences in time metrics between the prehospital teleconsultation group versus the traditional EMT group. Van Hooff et al [62, 63] demonstrated that remote assessment of stroke severity, using the unassisted telestroke scale in Belgium, is both feasible and reliable.

Portable digital assistant devices such as smartphone video teleconferencing for an NIHSS examination have also been demonstrated to be feasible and reliable [35, 64].

## Telestroke neurologists vs radiologists

Another pivotal component of clinical decision-making in acute stroke care is the review of neuroimaging, particularly CT scans to assist decision for interventions [65]. It is therefore important to determine reliability in neuroimaging interpretations between telestroke neurologists and neuroradiologists as it may have therapeutic impact.

In a review of imaging data from 536 patients enrolled in a single center telestroke network in Germany in which noncontrast head CT as quantified in Alberta Stroke Program Early CT Score (ASPECTS) for early ischemic changes were evaluated by stroke specialists using telemedicine and by 2 neuroradiologists blinded to clinical information providing reference standard [55]. Of 536 patients, 351 had cerebral ischemic events, 105 had primary intracranial hemorrhages, and 80 stroke mimics. The neuroradiologists detected discrepant CT findings in 43 patients (8.0%) that were rated as clinically relevant in 9 patients (1.7%). Stroke neurologists recommended IV thrombolysis in 8 patients despite extensive early ischemic changes (ASPECTS ≤5). One of these patients had symptomatic intracranial hemorrhage. The interobserver agreement on ASPECTS between stroke neurologists and expert readers was substantial (kw = 0.62; 95% confidence interval 0.54–0.71) suggesting that clinically relevant misinterpretation of the CT scans was rare, and that ASPECTS is a reliable tool to assess the extent of early ischemic changes by stroke neurologists in telemedicine in real time [55].

Similarly, in a pooled analysis two telestroke trials, The Stroke Team Remote Evaluation Using a Digital Observation Camera (STRokE DOC and STRokE DOC-AZ TIME), CT scans of the subjects were interpreted by the hub vascular neurologists compared to spoke radiologists [66]. Among 261 analyzed cases, the agreement with central readings for the presence of neuroimaging tPA contraindications was excellent for the hub vascular neurologist (96.2%, keppra = 0.81, 95% CI 0.64–0.97) and the spoke radiologist report (94.7%, k=0.64, 95% CI 0.39–0.88), and overall (95.4%, k=0.74, 95% CI 0.59–0.88). For tPA–treated patients (N= 65), overall agreement was 98.5%, and vascular neurologist agreement with central reading was 100% [66], suggesting that vascular neurologists and reports from spoke radiologists had excellent reliability in reading neuroimaging. However, these studies have not compared the accuracy of image interpretation by stroke neurologists or other nonradiologists as a function of their level of training and experience. Further high-quality studies are needed to define the minimum level of training and expertise required by an individual physician to achieve results in acute brain imaging interpretation similar to that of a stroke specialist.

Evidence indicates that teleradiology systems approved by the Food and Drug Administration (FDA) or equivalent organizations enable effective and rapid evaluation of images by stroke specialists in support of decisions on administration of tPA (class I recommendation, level of evidence B) [49]. The 2013 AHA guideline for acute stroke management states that “implementation of telestroke consultation in conjunction with stroke education and training for health-care providers can be useful in increasing the use of

intravenous tPA at community hospitals without access to adequate on-site stroke expertise" (class IIa recommendation, level of evidence B) [3].

## MOBILE STROKE UNIT

Time is of the essence in both acute coronary syndrome (ACS) and cerebral infarct. Endovascular reperfusion therapies for acute myocardial infarction (AMI) and ischemic stroke evolved in parallel: Beginning for intravenous fibrinolysis, followed by intra-arterial fibrinolysis, then progressing to mechanical thrombectomy. Figure 2 compared reperfusion rates of coronary artery vs cerebral artery endovascular trials. The concept of tissue-time in heart attack and brain attack prompted both Cardiology and Vascular Neurology to initiate prehospital therapy in the ambulance to maximize outcome.

### Prehospital electrocardiogram (EKG) analogy

Prehospital triage and identification of patients with ACS are critical since each minute of delay from symptom onset to intervention for increases mortality [67, 68]. Studies have shown that abnormal prehospital EKG signs of ischemia (ST elevation, ST depression, T-wave inversion) drive early treatment decisions for patients with myocardial infarction such as the decision to route the ambulance to what may be the closest hospital for a further one that offers definitive cardiac treatment [69]. Moreover, EKG signs of ischemia are independent predictors of adverse hospital outcomes, a final diagnosis of ACS, and direct admission to acute coronary care units [70, 71]. With these evidences, conducting a prehospital EKG while in the ambulance is becoming the standard of care and the American Heart Association designated prehospital EKG as a class I recommendation in its 2010 Cardiac Life Support guidelines [68].

### Stroke Emergency Mobile (STEMO)

Analogous to prehospital EKG that enables earlier diagnosis for AMI, noncontrast head CT enables earlier ischemic vs hemorrhagic stroke diagnosis. Amobile stroke unit is equipped with CT scanner, point-of- care laboratory, telestroke connectivity, thrombolysis capability, CT technician, EMT with or without a stroke neurologist [72]. Figure 3 shows the interior of a mobile stroke unit. Deployment of the mobile stroke unit might potently reduce time to treatment by allowing prehospital identification of patients with probable large artery occlusion, facilitating their in-hospital treatment by prehospital notification, earlier assembly of the endovascular team and angiography suite preparation, and shorter in-house delays incurred by acquiring imaging and laboratory data and treating with tPA, perhaps allowing bypass of ED evaluation altogether.

Germany developed a prototypic mobile stroke unit, called Stroke Emergency Mobile (STEMO) [72, 73]. Ebinger et al in 2014 published the landmark trial: Prehospital Acute Neurological Treatment and Optimization of Medical care in Stroke Study (PHANTOM-S) [74], which tested the effects of mobile stroke unit equipped with a CT scanner; point-of-care laboratory capability; telemedicine connectivity; and physician, paramedic, and CT technician responding to emergency alarms to the Berlin Fire Brigade in parallel with conventional ambulance dispatch. Figure 3 shows an example interior of a mobile stroke

unit. Over a 21-month period, the STEMO was dispatched every other week 1804 times, and 177 patients were treated with tPA in the ambulance prior to transport to the ED. The intervention resulted in a 25-minute reduction in time from alarm to tPA treatment compared with non-STEMO weeks (95%CI, 20 to 29-minute; $P < 0.001$), with 58% of patients treated within 90minutes of symptom onset (vs 37% in control), low rates of symptomatic intracerebral hemorrhage (2.2%), and notably no instances of CT malfunction. No differences were seen in discharge status, but the study was not powered or designed to assess clinical outcomes other than safety [74]. PHANTOM-S affirmed that prehospital delivery of tPA significant shortens the time of tPA administration from symptom onset, culminating a 20-year concerted effort for prompt and prevalent administration of tPA (Figure 4).

As mentioned earlier, apart from administering prehospital thrombolysis (Figure 1), prehospital diagnosis made inside of the mobile stroke unit could also enable disease-specific management in the field, and early triage with targeted ambulance routing to hospitals with specialized care. In a post-hoc analysis of PHANTOM-S, Wendt et al [75] aimed to evaluate whether prehospital management in the STEMO improves the triage of patients with stroke. They found that 11.6% of patients with cerebrovascular events were sent to hospitals without Stroke Unit in conventional care when compared with 5.5% patients in STEMO care (P<0.01). In patients with ischemic stroke, STEMO care reduced transport to hospitals without Stroke Unit from 10.1% to 3.9% ($P$<0.01). The delivery rate of patients with intracranial hemorrhage to hospitals without neurosurgery department was 43.0% in conventional care and 11.3% in STEMO care ($P$<0.01). There was a slight trend toward higher rates of patients discharged home in neurological patients when cared by STEMO (63.5% versus 60.8%; $P$=0.096) [75]. The study provided clear evidence that prehospital triage of patients with cerebrovascular events improved ambulance routing to specialized hospitals.

Future studies are needed to exam the short-term and long-term clinical outcomes of a mobile stroke unit. Houston developed the first mobile stroke unit in the United States. BEnefits of Stroke Treatment Delivered Using a Mobile Stroke Unit (BEST-MSU), is an ongoing trial led by Grotta et al. comparing outcomes (time from stroke onset to tPA treatment and 90-days mRS) with or without stroke neurologist onboard of the mobile stroke unit vs telestroke [76]. Future studies are also needed to test feasibility and utility of prehospital administration of neuroprotective to stabilized penumbra and thrombolytic enhancers to optimize durable recanalization.

## NEUROPROTECTIVES

Developing ways to improve reperfusion therapy for acute ischemic stroke has long been an active area of research in the past 3 decades with countless failures, and also more encouragingly, recent successes. Neuroprotective therapies for patients with acute ischemic stroke are treatments that enable brain cells to endure injury from reduced blood flow [77–80]. Neuroprotective agents block the molecular, cellular injury in hypoxic–ischemic tissues. Often safe in hemorrhagic (except thromoblytics) as well as ischemic stroke, many neuroprotective agents can be given prior to brain imaging, including in the prehospital

setting. By stabilizing threatened brain tissue, early neuroprotective therapy may increase the volume of salvageable tissue that is still present at the time that reperfusion therapy can be started, after hospital arrival and initial brain imaging.

Categories of neuroprotective agents have grown to include the following: suppressors of neuronal metabolism, calcium entry blockers, excitotoxic neurotransmission blockers, free radical scavengers, nitric oxide–related interventions, apoptosis inhibitors, hyperpolarization agents that inhibit peri-infarct depolarization, promoters of membrane repair, anti-inflammatory and anti-cytokine agents, and neurotrophic agents [80, 81]. More than 70 neuroprotective agents have been tested in more than 140 randomized, controlled, clinical trials in acute ischemic stroke, enrolling over 25,000 patients, but no agent was unequivocally beneficial in definitive phase III trials [82]. A key reason for failures was marked delay in delivery of neuroprotective agents in previous clinical trials. Preclinical trials in rodent and nonhuman primate experimental suggest the duration of the therapeutic window within which neuroprotective intervention can ameliorate bioenergetic failure in the ischemic penumbra is very brief, generally less than 2–3hours. Most animal studies of neuroprotective agents initiate therapy within 1–60 minutes after ischemia onset [80]. Unfortunately, overwhelming majority of neuroprotective trials had time to randomization up to 48-hours, well after the critical period for stabilizing the penumbral region had ended. An analysis of 5345 patients enrolled in six neuroprotective trials performed in the 1990s and 2000s showed that only 0.2% of patients received the study agent in the first hour after symptom onset and only 1.2% in the second hour; 6.3% received the agent in the third hour; and 92.3% were treated beyond 3 hours [83].

Prehospital therapy has been proven beneficial for other acute neurologic conditions. In status epilepticus, the Prehospital Treatment of Status Epilepticus trial showed that paramedic initiation of anticonvulsants in the field is safe, reliable, and yields better clinical outcomes than standard in-hospital therapy [84]. In cardiac arrest and global cerebral ischemia, the Melbourne hypothermia trial showed benefit of neuroprotective temperature reduction initiated in ambulances before hospital arrival [85]. Finally 2015 in stroke, The Field Administration of Stroke Therapy– Magnesium (FAST-MAG) [16], a pivotal phase 3 trial was published affirming the feasibility of administering prehospital acute stroke treatment within 2 hours after the onset of symptom during when neuroprotective agents and thrombolytic agents exert most effects on stroke outcomes. In the following section, we’ll describe intervention clinical trials of several prehospital stroke therapeutics, including neuroprotectives (magnesium sulfate, NA-1), antihypertensives (glyceryl trinitrate, lisinopril), collateral enhancement (volume expansion), thrombolysis enhancements (glycoprotein IIb/IIIa eptifibatide, thrombin inhibitor argatroban, and transcranial Doppler ultrasonography with or without microbubbles).

## Magnesium

Magnesium exerts both vasodilatory and direct neuroprotective and glioprotective effects in cerebrovascular disease by impeding calcium influx into ischemic neurons and prevents cell death [80, 86, 87]. It is also inexpensive and widely available clinically. Numerous preclinical models of stroke had shown benefit. FAST-MAG is a randomized, placebo-

controlled trial enrolled 1700 patients presented with acute ischemic stroke with a mean pretreatment score on the Los Angeles Motor Scale of stroke severity of 3.7±1.3 (range, 0 to 10, with higher scores indicating greater motor deficits) [16]. Ischemic stroke was found in 73.3% of patients, intracranial hemorrhage in 22.8%, and a stroke-mimicking condition in 3.9%. The median time to treatment from symptom onset was 45 minutes (interquartile range [IQR] 35–62), and 74.3% of patients received the study-drug infusion within the first hour after symptom onset. There was no significant shift in the distribution of 90-day disability outcomes on the global modified Rankin scale (mRS) between patients in the magnesium group and those in the placebo group (P = 0.28); mean scores at 90 days did not differ between the magnesium group and the placebo group (2.7 in each group, P = 1.00). No significant between-group differences were noted with respect to mortality (15.4% in the magnesium group and 15.5% in the placebo group, P = 0.95) or all serious adverse events [16]. While FAST-MAG did not show benefit in improving 90-days disability, it was a pivotal trial proving that it is possible to conduct prehospital clinical studies in ambulance, open the door for future prehospital study within the ‘golden hour’ when neuroprotectives and thrombolysis are most effective in stroke care.

### NA-1

NA-1 is another promising neuroprotective agent. It is a cell-permeant eicosapeptide that perturbs the protein–protein interactions of PSD-95, a postsynaptic scaffolding protein [88]. PSD-95 links NMDA glutamate receptors to neurotoxic signaling pathways, and NA-1 disrupts these links and inhibits stroke damage [89, 90]. Preclinical studies have shown that NA-1 reduces the volume of strokes after middle cerebral artery occlusion and reduces the volume and number of strokes after the intra-arterial injection of small emboli [91]. Evaluating Neuroprotection in Aneurysm Coiling Therapy (ENACT) [92] is a double-blind, randomized-controlled study to assess whether NA-1 would reduce the volume and number of periprocedural ischemic stroke in those with ruptured or unruptured intracranial aneurysm. Authors found that patients in the NA-1 group sustained fewer ischemic infarcts than did patients in the placebo group, as gauged by diffusion-weighted MRI (adjusted incidence rate ratio 0.53, 95%CI 0.38–0.74) and fluid-attenuated inversion recovery MRI (0.59, 0.42–0.83). As for ischemic stroke, Field Randomization of NA-1 Therapy in Early Responders (FRONTIER) [93] is an ongoing trial to assess if NA-1 may have neuroprotective effects on stroke functional outcome.

## ANTIHYPERTENSIVES

Antihypertensives may have a role in both ischemic and hemorrhagic stroke. In ischemic stroke, elevated blood pressure above 185/110 mmHg remains a common reason for withholding IV tPA, early initiation of antihypertensive therapy to reach this goal SBP in order to administer tPA is supported by positive results in multiple clinical trials [2, 94]. In intracranial hemorrhage, studies using CT imaging report hematoma growth in greater than 70% of patients within the first three hours of symptom onset [95] with only 11–12% expanding after the first three hours [96]. Treatment outside of this phase is unlikely to yield significant effect on outcome, and the earliest time windows for treatment, including pre-hospital treatment of blood pressure may be needed to prevent clinical deterioration and

obtain optimum clinical results. Clinically, as many as three in ten patients who are initially alert during paramedic evaluation within the first two hours of onset will have significantly deteriorated before arrival to the hospital [97].

Glyceryl trinitrate (GTN) has also demonstrated neuroprotective and antihypertensive properties in preclinical stroke models. GTN acts as an inhibitor of apoptosis [98] through formation of nitric oxide equivalent molecule that nitrosylates the redox modulatory site at the NMDA receptor. This has the neuroprotective effect of inhibiting NMDA receptor-mediated neurotoxicity [99]. In cerebral ischemia reperfusion models, administration of NO donor was shown to decrease free radical levels and reduce brain infarct volume [100]. Additionally, transcranial Doppler and xenon CT studies of cerebral blood flow have shown that transdermal GTN increases or maintains cerebral perfusion in acute ischemic stroke patients despite decreases in mean arterial pressure [101, 102].

Efficacy of Nitric Oxide in Stroke (ENOS) [103] is a large multicenter, randomized, placebo-controlled trial enrolling about 2000 patients in each arm presented with acute stroke symptoms within 3 hours, systolic blood pressure of 140–220mmHg, could be treated with 7 days of transdermal glyceryl trinitrate (5mg daily) or placebo within 48 hours of symptom onset. There was no difference in 90-days mRS (odds ratio 1.01, 95%CI 0.91–1.13, P=0.83) between the groups. However, subgroup analysis showed favorable 90-days outcomes among those receiving glyceryl trinitrate within 6-hours after symptom onset (P=0.031) suggesting that transdermal GTN may have a role in prehospital stroke treatment [103].

Indeed, in Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT) [104] is a small randomized-controlled trial involving 80 patients (25 GTN, 16 no GTN) done in the ambulance within less than 4 hours of stroke onset. Systolic blood pressure at 2 hours was 153±31mmHg vs 174±27mmHg (P=0.04), in GTN vs no GTN groups, respectively. The mean 90-days mRS was 3 vs 5 (P=0.17), 90-days mortality was 15% vs 38% (P=0.15), and adverse events: 56% vs 63% (P=0.75). The trial demonstrated that paramedics can successfully enroll patients with ultra-acute stroke into an ambulance-based trial and that GTN reduces systolic blood pressure at 2 hours and seems to be safe in ultra-acute stroke. Similarly, Paramedic Initiated Lisinopril For Acute Stroke (PIL FAST) is another double-blind RCT testing the effect of prehospital administration of Lisinopril vs placebo on BP treatment. Median time from stroke onset to treatment was 70minutes [105]. The study again demonstrated feasibility of prehospital hyperacute stroke treatment.

## REMOTE ISCHEMIC PRECONDITIONING

Remote ischemic preconditioning (rPerC) is a novel prehospital therapeutic (under investigation) by which sublethal ischemic stimulus is administered during the ischemic event that have shown promising outcomes in pilot human trials for myocardial infarction [106] and ischemic stroke [107]. The protective effect of rPerC involves the activation of multiple endogenous defense mechanisms including increased nitric oxide levels, improved cerebral blood flow in the ischemic penumbra, and decreased inflammation and glutamatergic excitotoxicity [108].

In a randomized-controlled trial, Hougaard et al [107] tested the effect of prehospital rPerC as an adjunct to treatment with intravenous alteplase in patients with acute ischemic stroke in prehospital setting by ambulance staff. rPerC was induced by 4 cycles of inflations of a standard upper limb blood pressure cuff to either 200mmHg or 25mmHg above the patient's systolic blood pressure. Compared to the control, patients received rPerC had no statistically significant effect on salvage, infarct size, or infarct progression as measured by MRI at 3-month. After adjustment for baseline perfusion and diffusion lesion severity, voxelwise analysis showed that rPerC reduced tissue risk of infarction ($P$=0.0003) [107]. Ongoing trials are investigating the effective duration and application of rPerC.

## COMBINED THERAPIES FOR THROMBOLYSIS ENHANCEMENT

Combined therapeutics is another promising prehospital therapeutic that could be co-administered in the mobile stroke unite to improve sustained recanalization and stroke outcome. IV thrombolysis alone opens about 50% of occluded arteries, paradoxically, lysis of an occluding clot has prothrombotic effect such that 14–34% of these re-occlude within 2 hours leading to worse outcomes [109–111]. Rupture of plaque releases a pool of trapped thrombin and exposes tissue factor, surface-bound von Willebrand factor and collagen, which activate the intrinsic and extrinsic coagulation cascades. Optimal reperfusion treatment may require several components including antiplatelet and antithrombin agents, in addition to fibrinolytic drug, in order to prevent re-thrombosis [112]. Combined pharmacotherapy for thrombolysis enhancement have been described in Cardiology literature. In stroke, combination pharmacotherapy strategies to expand the intravenous fibrinolysis time window beyond 4.5 hours are currently under active investigation. A rational combination of agents with additive effects on clot lysis and clot formation may yield higher rates of arterial recanalization, lower rates of re-occlusion, reductions in the dose of fibrinolytic agent required, and reduced frequency of hemorrhage transformation. Furthermore, combining neuroprotective therapies with fibrinolytics may potentiate treatment benefit and extend the time window in which salvageable tissue persists to be rescued by reperfusion [113].

### Thrombolysis plus thrombin inhibitor (argatroban)

Argatroban in a thrombin inhibitor that directly and selectively inhibits free and clot-associated thrombin. Safety of argatroban has been demonstrated with thrombolytics or aspirin in patients with acute myocardial infarction with major bleeding risk of 2.6% and 4.6% for low-dose and high dose-argatroban, lower than the control of 10% [114]. Unlike the soft pericardial sac that surrounds the heart, the brain is encased in hard skull of which hemorrhagic conversion is a neurologic emergency that can be life-threating. Careful evaluation of intracranial bleeding risk is necessary prior to applying combined tPA and argatroban clinically. In animal stroke models, argatroban safely augments the benefit of tPA by improving flow in the microcirculation, increasing the speed of clot lysis.

The Argatroban tPA Stroke Study (ARTSS) [115] is a pilot safety study of full-dose IV tPA (0.9 mg/kg) enrolled 65 patients in a prospective, single arm trial of combined standard dose IV tPA plus argatroban infused for 48-hour adjusted to a target partial thromboplastin time

(PTT) 1.75 times of baseline. Among the first 20 patients enrolled, symptomatic intracerebral hemorrhagic rates were low (4%). Partial or complete recanalization at 2-hour was achieved in 70% of patients. Complete recanalization at 2-hour trended higher in the combined argatroban plus tPA group than in historical controls (35% vs. 13%). The pilot study showed that combined argatroban and tPA is potentially safe in patients with moderate neurological deficits due to proximal intracranial arterial occlusions and may produce more complete recanalization than tPA alone [115]. Phase IIb of ARTSS-2 is ongoing to further evaluate safety and efficacy along with another trial, Minimizing Onset of Stroke Treatment Time stroke trial (MOST) [116].

### Thrombolysis plus platelet inhibitor GPIIb/IIIa (eptifibatide)

Glycoprotein (GP) IIb/IIIa antagonists potently block the platelet GP IIb/IIIa receptor, the final mediator of aggregation. GP IIb/IIIa a reduce thrombus growth and prevent re-occlusion after mechanical or lytic-driven recanalization. Moreover, GP IIb/IIIa antagonists have the ability to dissolve platelet-rich clots and to improve flow in coronary and cerebral microcirculation [113]. In practice, GPIIb/IIIa inhibitors are commonly used in high-risk acute MI and to prevent percutaneous coronary stent occlusion [117]. Combination GP IIb/IIIa inhibitors plus IV thrombolysis resulted in higher rates of thrombolysis in myocardial ischemia 3 reperfusion (compared with non-GPIIb/IIIa arms) in Phase II studies [117].

Eptifibatide is a highly selective GP IIb/IIIa antagonist tested in combination with tPA within 3 hours of onset in a multicenter phase 2 dose-escalation study involving 126 patients (CLEAR-ER) [118] randomized to the intervention group who received 0.6 mg/kg tPA plus eptifibatide (135 mcg/kg bolus and a 2-hour infusion at 0.75 mcg/kg per minute) and the control group who receive 0.9 mg/kg tPA. The 90day mRS 0–2 was 49.5% vs 26% with odds ratio of 1.74 (95%CI 0.7–4.3, P=0.23) [118]. The study demonstrated that enhanced dosing regimen of medium-dose tPA combined with a bolus followed by a short infusion of eptifibatide studied in this trial proved to be safe compared with standard-dose tPA [118].

### Thrombolysis plus transcranial Doppler (TCD) ultrasound

Experimental and clinical studies have consistently demonstrated the capability of ultrasound to enhance enzymatic thrombolysis [119]. Ultrasound application increases the transport of tPA into the thrombus, promotes the opening and cleaving of the fibrin polymers, and improves the binding affinity of tPA to fibrin. While low frequency ultrasound in tandem with tPA has been found to increase the risk of brain hemorrhage [120], high frequency ultrasound of the type used in standard diagnostic studies has appeared safe and potentially beneficial. Higher frequency ultrasound with microbubble seem to induces further acceleration thrombolysis resulting even more complete recanalization in large-vessel occlusive stroke [121].

Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic tPA (CLOTBUST) is a phase 2 multicenter randomized trial, demonstrated that 2-h continuous application of 2 MHz transcranial Doppler (TCD) ultrasound in tandem with tPA is safe and may improve outcome [110]. Among 126 patients randomized to tPA plus 2-h TCD monitoring (target group) or tPA alone (control group), symptomatic ICH occurred in

4.8% of target and 4.8% of control patients. Complete recanalization or dramatic clinical recovery at 2 h after tPA bolus was observed in 49% of target and 29% of control patients (P = 0.02) [110]. The study demonstrated that continuous TCD ultrasound augments t-PA-induced arterial recanalization, with a nonsignificant trend toward an increased rate of recovery from stroke, as compared with placebo.

A major drawback of the stand diagnostic TCD ultrasound is that it is operator dependent, required a skilled sonography to position the ultrasound window over the target clot. An ongoing trial, CLOTBUST-HF (Hands-Free) [122, 123] will instead test a novel, continuous wave Doppler device that can be placed by any health professional. The clot disrupting effects of ultrasound energy can be potentiated by the addition of gaseous microsphere ultrasound contrast agents, which resonate, expand, oscillate, and detonate near and within the thrombus when subjected to externally applied ultrasound. In the feasibility study, the hands-free TCD device was well tolerated by stroke-free volunteers and did not cause any neurological dysfunction nor did it affect blood brain barrier integrity. If the trials turn out to be positive, it may offer a novel means to enhance thrombolysis in prehospital settings [122, 123]

## COST EFFECTIVENESS

The MSU strategy could dramatically transform the way acute stroke is managed in the United States, but there are important gaps that need to be addressed prior to widespread implementation of MSU. These include the ability to adapt the MSU to the logistics of the more complex US health care system, reliability of telemedicine on the MSU, clinical outcomes, and costs. These are being addressed by a trial executed in the United States [124, 125].

The initial costs to set up mobile stroke unit including purchasing, equipping, and deploying an ambulance with a CT scanner, point-of-care laboratory testing capabilities, telemedicine, and other needed equipment in Houston has cost approximately $600,000. The cost, however, should be balanced with the costs against the total hospital and long-term care costs to the health care system for each patient with an ischemic stroke, estimated to average approximately $140 000 per patient in 1990s dollars, likely be much higher today [126, 127].

There are undoubtedly geographical disparities in the delivery of stroke thrombolysis with studies showed that patients with acute ischemic stroke presenting to rural emergency departments are ~10-times less likely to receive tPA than those presenting to urban primary stroke centers [54]. While mobile stroke unit may bring stroke expertise and prehospital therapeutics to underserved regions, no study has investigated how the cost effectiveness of mobile stroke unit may be influenced by the incidence of stroke in the community such as rural vs urban community, developed vs developing countries. Studies are needed to address the cost and effectiveness of mobile stroke units in various communities.

## EXPERT COMMENTARY: CURRENT STATUS OF THE FIELD

PHANTOM-S and recent endovascular trials have changed the landscape of acute stroke treatment in a very short time. Mobile stroke units will likely disseminate the use of tPA now 20-years after FDA approved its use for ischemic stroke. With a mobile stroke unit, many more patients receive tPA within 60-minutes of symptom onset (31% vs 5% comparing STEMO vs conventional ambulance) [73]. Early diagnosis using CT will also enable targeted ambulance routing to hospitals with specialized care, which intuitively will likely improve patient outcome. Studies are needed to evaluate the impact of ambulance–based prehospital therapy on functional outcomes. There is great concordance in the interpretation of neuroimaging between telestroke neurologists and radiologists also with evidence supporting an increased tPA administration through telestroke. With advancement in wireless/broadband telecommunicate and fast transmission of neuroimaging, telestroke will bring stroke expertise to resource limited regions, narrowing disparities in the delivery of stroke care. FAST-MAG is another landmark trial proving that it is possible administer neuroprotective agents within 2 hours after the onset of symptom during when neuroprotective agents and thrombolytic agents exert are most effective. This opens an era of research into the golden hour to evaluate the true effect of neuroprotective agents that may had failed in the past due to delayed treatment.

## FIVE YEARS VIEW

There is very little information on how much improvement in clinical outcomes will occur with treatment within the first 60 to 80 minutes after onset of stroke. Faster treatment using the mobile stroke unit (MSU) will allow us, to answer an important scientific question by making treatment possible within the golden hour after symptom onset when tPA is likely to have its greatest effect [124]. Future of acute stroke will perhaps shift to prehospital treatment with clinical trials evaluating the feasibility of neuroprotective agents to prolong therapeutic window to reperfusion therapy, or and combined tPA with thrombolysis enhancers such as antiplatelet/anti-thrombin agents administered within the golden hour to ensure complete and sustained recanalization.

No studies in the United States have specifically evaluated the economic impact of having a CT scanner in MSU to improve early tPA administration. It is therefore unclear whether it will ever be financially rational to install a CT scanner in all ambulances. Perhaps in five years, there will be biomarkers with the same sensitivity as CT to differentiate ischemic from hemorrhagic strokes that enable prehospital tPA, which may likely be more cost-effective than widespread CT scanner in the ambulance.

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## KEY ISSUES

- Rapid intravenous thrombolysis treatment and patient selection are keys to optimal stroke outcomes
- Telestroke is a feasible (and reliable) mean to improve remote access to stroke experts, and thereby increases tPA administration rate, and shortens time to tPA treatment
- There is acceptable interrater agreement between telestroke neurologist and neuroradiology on neuroimaging interpretations to validate rapid transmissions of neuroimaging in Telestroke
- Mobile stroke unit (MSU) equipped with CT scanner, point-of- care laboratory, telestroke enables early stroke diagnosis, rapid tPA treatment, and early triage with targeted ambulance routing to hospitals with specialized care
- Studies to evaluate the impact of mobile stroke unit on long-term clinical outcome are needed.
- Centers around the world will need to customize their prehospital treatment via Mobile Stroke Unit to fit the characteristics and limitations of their communities
- Prehospital stroke management enables treatment trials in the “golden hour” when neuroprotective and neuro-therapeutic agents may be most effective.
- Thrombolysis enhancers like transcranial ultrasonography or combined thrombolysis with anti-platelets or antithrombin may prevent re-occlusion after reperfusion therapy

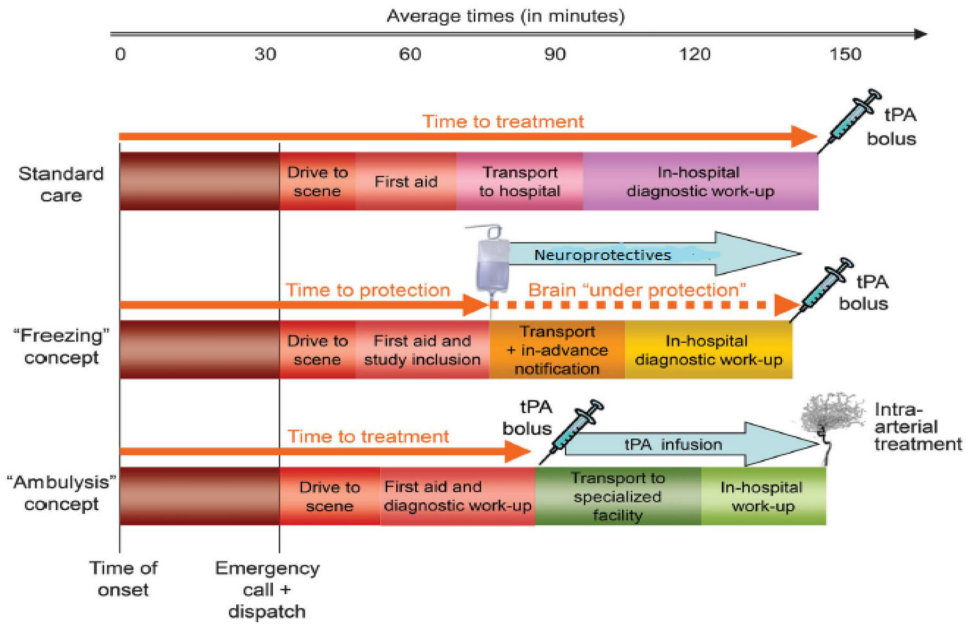


**Figure 1.**

The first row represents standard care with hospital-based diagnostic workup and treatment. The second row illustrates the "freezing" concept like with application of a neuroprotective agent by paramedics and delivery of patients after prenotification of hospital-based stroke teams. The third row exemplifies the "ambulysis" approach with prehospital brain imaging and point-of-care laboratory, starting IV thrombolysis in the field, and transport of patients to specialized facilities for interventional treatment (if indicated). tPA: tissue plasminogen activator. Image adopted and modified with permission from Audebert H, et al. Neurology. 2013;81:501–508.

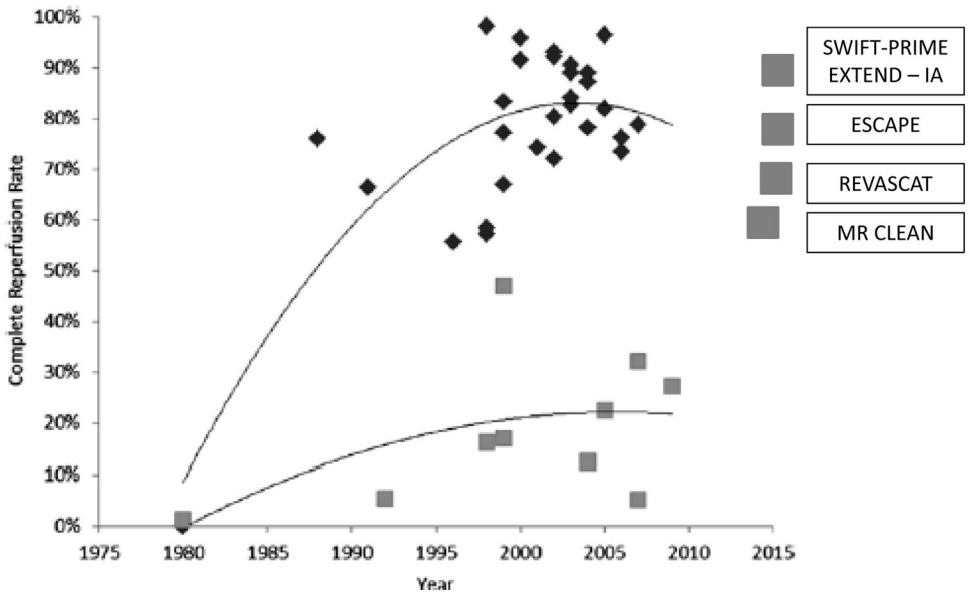


**Figure 2.**

Trends over time in complete reperfusion rates in active arms of coronary (diamond), cerebral (square) , and 2014–2015 cerebral (large square) reperfusion trials . Image adopted and modified with permission from Patel R and Saver J. *Stroke.* 2012;44:94–98.


**Figure 3.**
Interior view of Mobile Stroke Unit (MSU) with CT-scanner, point-of-care laboratory telestroke and thrombolysis capabilities. Image adopted with permission from Audebert H, et al. Neurology. 2013;81:501–508.

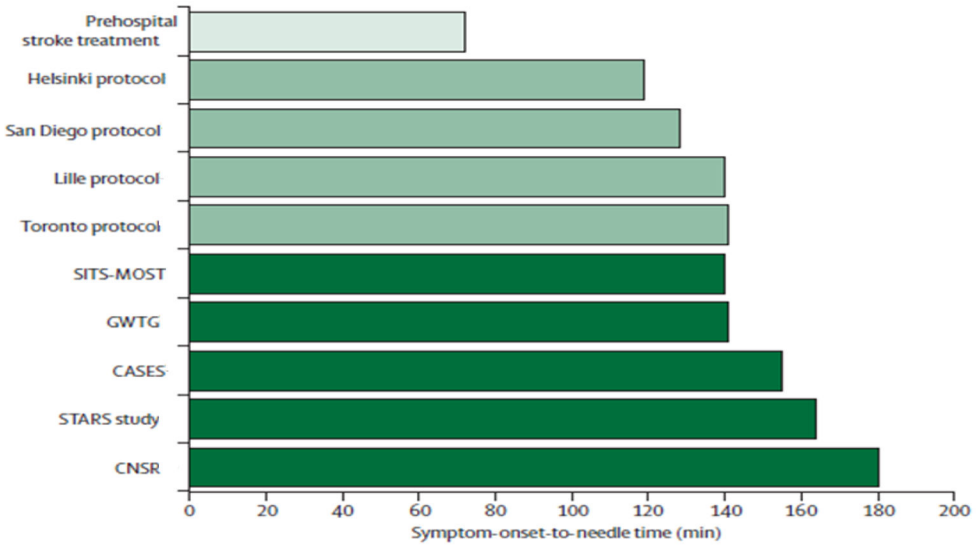


**Figure 4.**

Comparison of median times between symptom onset and tPA administration achieved by the strategy of prehospital stroke treatment with those reported in previous interventional studies and large stroke treatment registries. CNSR=Chinese National Stroke registry. STARS=Standard Treatment with Alteplase to Reverse Stroke. CASES=Canadian Alteplase for Stroke Effectiveness Study. SITS-MOST=Safe Implementation of Thrombolysis in Stroke-Monitoring Study. GWTG=Get With the Guidelines Stroke registry (subpopulation of patients transported by EMS with prenotification or the receiving hospital). Prehospital stroke treatment is the comparator. Light green bars show interventional studies, and dark green bars show registries. Image adopted and modified from Fassbender K et al. *Lancet Neurology.* 2013:12:585–96, with permission from Elsevier.